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BMJ Open Predictors of pain reduction following manual therapy in patients with temporomandibular disorders: a protocol for a prospective observational study

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ABSTRACT

Introduction Temporomandibular disorders (TMDs) are principally characterised by pain in the craniomandibular area and probable limitations of jaw opening. Manual therapy, like other recommended conservative treatments included in clinical guidelines, is commonly used to treat patients with TMD to reduce pain and improve function. However, outcomes may be variable. The aim of this study is to identify predictors associated with pain reduction in patients with TMD following manual therapy by analysing a combination of patient-reported outcome measures and clinical tests. Such knowledge will support a more personalised management approach by facilitating clinical decision-making.

Methods/analysis An observational prospective design will recruit a cohort of 100 adults with a diagnosis of TMD (according to Axis I of the Diagnostic Criteria for TMD) at a Dental Hospital in Italy. Patients will be treated with four weekly sessions of manual therapy applied to craniomandibular structures. An array of predictors has been chosen based on previous research on prognostic factors for TMD and altered pain modulation in musculoskeletal disorders. Candidate predictors including demographic variables, general health variables, psychosocial features, TMD characteristics and clinical tests of the temporomandibular joint and masticatory muscles will be collected at baseline. Definition of good outcome is a clinically significant reduction of pain intensity over the last week ($\geq 30\%$ reduction Visual Analogue Scale) immediately following the four week intervention. Exploratory factor analysis will be applied to analyse factor loading of candidate predictors for good outcome at four weeks. Subsequently, a logistic multivariable regression model will be performed to calculate low and high risk of good outcome.

Ethics and dissemination Ethical approval has been obtained from the 'Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico' and University of Birmingham Ethics Committee. The results will be submitted for publication in a peer-reviewed journal and presented at conferences.

Trial registration number NCT03990662; Pre-results.

INTRODUCTION

Temporomandibular disorders (TMD) affect ~10% of the adult population and, in the

Strengths and limitations of this study

- This will be the first study to identify predictors associated with pain reduction following manual therapy interventions in patients with temporomandibular disorder (TMD).
- The study will use a comprehensive array of candidate factors to predict clinically relevant pain reduction.
- The implications from this study will facilitate clinical decision-making for manual therapists managing patients with TMD.
- Alternative or additional predictors could be valuable to include but the candidate predictors have been prioritised as they are reliable and valid measures which have a relationship with pain.
- The study could potentially generate a non-representative sample of patients as it will exclude people who have already received recent treatment for their TMD.

USA alone, are estimated to cost US\$4 billion per year on management.^{1 2} In Spain, the incidence of TMD has significantly increased (from 8% in 1993 to 14% in 2015) despite a clear improvement in general oral health over the entire period.³ Although some countries report less prevalence of TMD such as in Sweden (~5%),⁴ TMD remains a public health-related challenge. TMD are principally characterised by pain and limitations of jaw opening⁵ but many patients also complain of neck and back pain or pain at other sites.⁶

Physical therapy is one of the most common conservative interventions for the management of TMD⁷ and given that the aetiology may be unclear,⁸ several therapeutic approaches have been described.⁹ One approach is manual therapy applied to the craniomandibular structures with evidence suggesting a significant reduction in pain with manual therapy treatment,¹⁰ although responses are highly variable.¹¹ In

other musculoskeletal pain disorders, such as neck or back pain, pain reduction from manual therapy has been shown to be superior to other treatments (eg, therapeutic exercise) when targeted towards patients with specific clinical features including the onset of symptoms within 30 days.^{12 13} Nevertheless, in TMD, no previous study has investigated patient factors associated with significant pain reduction following manual therapy. Such knowledge could be achieved by identifying potential predictors (eg, pain characteristics, psychosocial features, TMD characteristics) of pain reduction following manual therapy interventions in patients with TMD to support a more personalised management approach.

Very few studies have examined factors associated with pain reduction in patients with TMD. Forssell *et al* conducted a prospective cohort study with 263 primary care patients with TMD pain.¹⁴ They analysed several potential predictors of persistent pain at 1-year follow-up including demographic, pain-related and psychosocial variables. It was concluded that patients with TMD who have had numerous previous healthcare visits, complained of high-intensity pain at other body sites and had a greater number of disability days, were at greater risk of having pain 1 year after the initial assessment. Nevertheless, this study did not examine predictors of pain reduction related to a therapeutic intervention which could be useful to inform clinical practice. Kapos *et al* investigated the association of long-term pain intensity with baseline health-related quality of life and jaw functional limitation in patients with TMD.¹⁵ Findings suggested that baseline health-related quality of life is inversely proportional with pain intensity at an 8-year follow-up regardless of the type of treatment that they received (eg, surgery, drugs, physical therapy or unconventional therapy). After adjusting for the type of treatments received, by clustering the participants into three groups (medical/conventional management, complementary medicine and surgical intervention), each predictor analysed (demographic, pain-related and health-related quality of life) maintained similar statistical significance. Notwithstanding, the group classified as 'medical/conventional management' included participants receiving diverse treatments ranging from physical therapy, pharmacology (acetaminophen, antidepressants, anti-inflammatories) to the application of a mouth appliance (eg, Michigan splint). This previous work can facilitate clinicians to identify patients who are more challenging to treat by identifying clinical features associated with persistent pain in the long-term regardless of the type of interventions applied. However, currently no study has examined predictive factors associated with pain reduction following manual therapy interventions in patients with TMD.

The aim of this study is to identify predictors associated with pain reduction in patients with TMD following manual therapy applied to craniomandibular structures by analysing a combination of: (1) demographical variables, (2) general health variables, (3) psychosocial features, (4) TMD characteristics and (5) clinical tests of

the temporomandibular joint and masticatory muscles. The knowledge gained from this study will facilitate clinical decision-making for manual therapists managing patients with TMD by providing clinicians with key factors to evaluate, to determine whether or not the patient is likely to have a clinically relevant reduction in their pain immediately following 4 weekly applications of manual therapy.

METHODS AND ANALYSIS

Source of data

A prospective observational study will recruit a cohort of patients referred to the Italian Stomatologic Institute with a TMD diagnosis according to the Axis I of the Diagnostic Criteria for TMDs (DC/TMD).¹⁶ This protocol is written according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement¹⁷ in which recommendations are provided about prediction model development and validation. Ethical clearance will be obtained from the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and the University of Birmingham Ethics Committee, and the study will be conducted in accordance with the Declaration of Helsinki.

Patient reported and physical assessment data will be collected at baseline prior to commencing treatment. Outcome will be collected at the end of the fourth session of craniomandibular manual therapy (at 1 month). This timeline has been selected based on previous studies investigating (1) the effects of manual therapy on pain^{18 19}; and (2) work confirming the effectiveness of manual therapy for TMD patients²⁰ and is believed to be reasonable for the purposes of this study.

Setting and participants

Participant recruitment will be carried out at the TMJ Unit of the Italian Stomatological Institute (Dental Hospital) in Milan, Italy over a period of up to 12 months (planned start date July 2019). Consecutive eligible participants will be approached for recruitment until the sample size is reached.

Eligibility criteria

Inclusion criteria: (1) adults aged ≥ 18 years; (2) TMD diagnosis according to the Diagnostic Criteria for TMDs (DC/TMD)¹⁶; (3) no therapeutic interventions reported (for their TMD) in the last 6 months²¹; (4) capacity to use and understand written and verbal Italian language; (5) mental capacity to provide informed consent.

Exclusion criteria: (1) TMD pain related to rheumatoid/inflammatory arthritis (2) any physical (eg, facial paralysis, neurological disorders, neuropathic pain) or mental condition (eg, cognitive deficit, mental illness and/or disorders) that could potentially influence the study results. Additionally, patients will be excluded if (3) they commence another treatment for their TMD

(pharmacology, oral appliance, others) throughout the duration of the study.

Recruitment

Based on feasibility data from the last 5 years of activity at the TMJ Unit of Italian Stomatologic Institute, it is estimated that at least 130 eligible participants will be available for recruitment over 13 months. According to previous observational studies on the prediction of outcomes in musculoskeletal disorders,^{12 13} it is estimated that 75% of eligible participants will consent to participation (100 participants).

All patients attending the TMJ Unit will be screened for the presence of a TMD. One expert dentist with >10 years' experience in the management of patients with TMD, will confirm the TMD diagnosis according to the DC/TMD using the Italian translation of the protocol.²² Subsequently, in accordance with the inclusion/exclusion criteria, he will explain the study to the potential participant and provide the patient information sheet. Participants will then give their written informed consent prior to inclusion in the study. Afterwards, the participant will be referred to see a physiotherapist (independent assessor, >5 years' experience in managing patients with TMD) for the baseline assessments (summarised in table 1) and then treatment will commence within the same week. After the last session (ie, 1 month from baseline), the participants will be assessed again by the assessing physiotherapist to measure outcome. Participant flow through the study is outlined in figure 1.

Treatment

Participants will receive four sessions of manual therapy applied to craniomandibular structures over 4 weeks^{23–25}. Two physiotherapists, each with >5 years' experience in manual therapy/TMD will perform the treatments. They will not be involved in participant recruitment, assessment or the collection of the outcome measure. Manual therapy techniques will be based on the clinical examination, and will be selected at the discretion of the treating physiotherapist according to their clinical reasoning of the individual case. Overall, the application of manual therapy aims to decrease pain by treating masticatory muscle trigger points, muscle tightness and restricted temporomandibular joint movements. Several techniques will be considered including: (1) ventral and caudal anterior glide temporomandibular joint mobilization²⁶; (2) soft tissue interventions for the management of trigger points in masticatory muscles²⁷; (3) myofascial induction therapy (functional restoration of the fascial system) applied to craniomandibular structures.²⁸

The structures targeted in the treatment sessions will be the temporomandibular joint, temporal muscles, masseter muscles, medial and lateral pterygoid muscles and suprahyoid muscles, applied at the discretion of the physiotherapist based on the patient's individual presentation. During the treatment sessions, the treating physiotherapists will provide explanations about the

patient's condition and answer any participant questions by promoting general advice. The treatment sessions will last from 20 to 30 min duration. No other treatment (eg, oral appliance) will be performed for the management of their TMD. If during the course of the 4-week intervention, a patient seeks treatment for an acute episode of pain at another site (eg, neck pain, low back pain, shoulder pain) they will be withdrawn from the study.

Outcome

The outcome being predicted by the prediction model is pain intensity since patients with TMD typically report pain to be their primary problem,⁵ manual therapy is largely known to be effective principally for pain modulation²⁹ and change in pain intensity has most commonly been the primary outcome of choice in several other studies of patients with TMD.^{30–33}

Pain intensity will be calculated by averaging the ratings of current pain, average pain in the last week, and worst pain in the last week using the Visual Analogue Scale (VAS), consisting of a horizontal line measuring 10 cm (without marks), with 'no pain' written at the left extremity, and 'worst pain imaginable' at the right extremity.³⁴ The VAS is a reliable and valid scale to assess pain intensity as an outcome measure in intervention studies.³⁵ Based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations about TMD reviewed by Haythornthwaite,³⁶ a reduction of at least 30% of the VAS score for pain intensity is considered clinically significant. Consequently, a reduction in the total VAS score ($\geq 30\%$) will be defined as a good outcome. The outcome measure will be evaluated by the same independent assessor to minimise detection bias.³⁷

To capture a potential change in function which may occur with a change in pain intensity, patients will also complete the patient-specific functional scale (PSFS)³⁸ pretreatment and post-treatment. The PSFS is a self-reported outcome measure assessing functional change in patients with musculoskeletal disorders.^{39 40} It is responsive to clinically significant change over time.⁴¹ Patients will be invited to rate, on an 11-point scale, their level of difficulty performing at least three different daily activities. Following the treatment, patients will be required to score again the activities previously rated. The PSFS is a valid, reliable, and responsive outcome measure with a high test-retest reliability in different musculoskeletal disorders such as low back and neck pain.^{42–44}

Candidate predictors

The candidate predictors that have been chosen are reliable and valid measures which have a relationship with pain. The selection is based on previous research on prognostic factors for TMD and altered pain modulation in musculoskeletal disorders.^{45 46} Candidate predictors are summarised in table 1, with further detail in online supplementary file S1. All data collection will be standardised through protocols and clinical report forms.

Table 1 Summary of candidate predictors

Domain / candidate predictor	Measure / data item
Demographical variables	
Age	Years
Gender	Female / male
Education	Basic education, intermediate education and university-level education
General health variables	
Health-related quality of life	EuroQol EQ-5D-5L ⁵²
Sleep quality	11-point (0–10) Numerical Rating Scales, relating to current pain, from ‘best possible sleep’ to ‘worst possible sleep’ ⁵³
Psychosocial features	
Coping strategies applied during a painful experience	Coping Strategies Questionnaire 27 (CSQ-27) ⁵⁴
Anxiety and depression	Hospital Anxiety and Depression Scales (HADS) ⁵⁵
Treatment expectation	Positive / negative expectation ⁵⁶
TMD characteristics	
Pain duration	Days
Pain intensity	VAS: averaging ratings of current pain, average pain and worst pain in the last week ⁵⁷
Pain location	Pain drawing as described in the protocol of Diagnostic Criteria for TMD (DC/TMD) ¹⁶
Central sensitisation	Central Sensitisation Inventory (CS) ⁵⁸
Classification of TMD	In according to DC/TMD Taxonomy ⁵⁹
Oral behaviours	Oral Behaviours Checklist (OBC) ⁶⁰
Characteristic pain intensity and disability	Graded Chronic Pain Scale (GCPS) version 2.0 (Italian version—www.rdc-tmdinternational.org)
Temporomandibular joint (TMJ) and masticatory muscles clinical test	
TMJ range of motion	Maximal Mouth Opening (MMO) without pain measured in mm through a ruler as described in the DC/TMD protocol ¹⁶
TMJ palpation pain	Dynamic TMJ lateral pole palpation (1 kg of palpation pressure) in according to DC/TMD protocol ¹⁶ Score range: 0–1 (no pain=0; pain=1)
Muscle palpation pain	Palpation in the following six bilateral points: lateral pterygoid area (0.5 kg intraoral palpation), temporalis tendon (0.5 kg intraoral palpation), masseter muscle (1 kg extraoral palpation) as described in the DC/TMD protocol. ¹⁶ Score range: 0–1 (<3 sites with familiar pain=0; ≥3 sites with familiar pain=1)
JAw-test	Immediate effects of brief intraoral MT techniques on pain (VRS) and TMJ range of motion (MMO). A standardised procedure is fully described in online supplementary file S1. Score range 0–2: (0=no change; 1=pain improvement or MMO improvement; 2=improvement of both)

VAS, Visual Analogue Scale; VRS, Verbal Rating Scale.

Data handling

Candidate predictors will be collected by independent physiotherapist assessor. All data will be confidentially secured by storing it on a password-protected computer attainable only by the principal investigators (GA). All individual details will be replaced with ID codes. At the end of the data collection, all data stored on the principal investigator's computer will be transferred securely to a server at the Centre of Precision Rehabilitation for Spinal Pain at Birmingham University where the data will be analysed. All data will be stored on a secure server at

the University of Birmingham for a period of 10 years in line with Research Governance procedures. Data will be analysed using IBM SPSS Statistics V.25.

Sample size

Exploratory factor analysis will be utilised to reduce the number of predictors.⁴⁷ This method will guarantee an adequate sample size (at least 10 cases per candidate predictor) to power the final regression analysis.^{48 49} Data will be collected for a sample size of 100 participants so

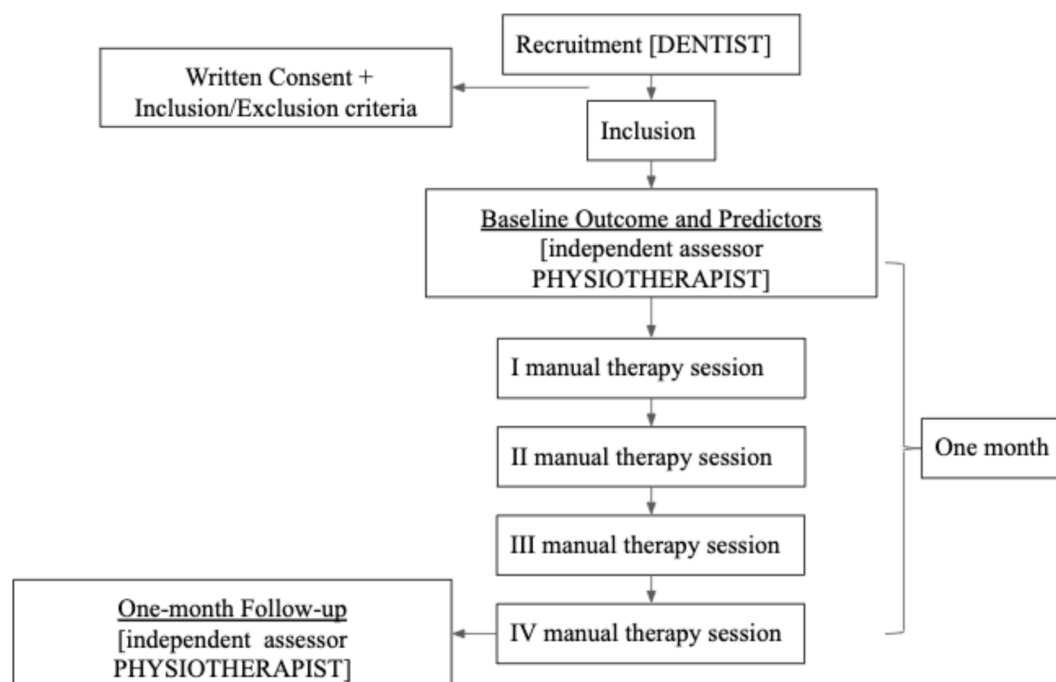


Figure 1 Participant flow through the study.

that, considering 10% of potential drops out, final data are available for 90 participants.

Statistical analysis methods

A flow diagram will report eligible participants, examined for eligibility, confirmed eligible, recruited into the study, completed follow-up and analysed. Reasons for non-participation, exclusion, drop-outs and withdrawal will be fully documented and all missing data of participants will be reported. Participant characteristics (candidate predictors—table 1) will be summarised with a descriptive method.

A primary phase of the exploratory data analysis will summarise data to implement the predictive model.⁵⁰ Multicollinearity between candidate predictors will be assessed at baseline. Outcome (VAS pain intensity) will be split into good versus poor as described previously (good outcome: reduction in VAS score $\geq 30\%$).³⁶ Exploratory factor analysis will be applied to analyse factor loading of candidate predictors (summary scores) on good outcome at 1 month. This process will reduce candidate predictors (supported by the cohort sample of 90) to enter into the final model.

The statistical model has been designed a priori. To investigate the impact of each predictive factor on good outcome, a logistic multivariable regression model will be performed. For each candidate predictor, the mean differences or the OR with their 95% CIs will be calculated. A multiple imputation analysis⁵¹ will be applied to manage possible missing data. The multivariable analysis will initially consider all candidate predictors. In the case of a high correlation between candidate predictors, a reduced multivariate analysis will be considered.

DISCUSSION

There is a need to identify predictors for pain reduction in patients with TMD following specific treatments in order to inform clinical decision-making. Several therapies are described for patients with TMD such as the use of oral appliances, different types of physical therapy modalities, pharmacology or temporomandibular joint arthrocentesis yet the amount of pain relief that different people receive from each intervention is variable.^{7 10} As shown by Forssell *et al*¹⁴ and Kapos *et al*,¹⁵ many patients continue to experience pain following such interventions. Investigating factors associated with pain relief to such treatments can facilitate clinical assessment and treatment selection.

Physical therapy is one of the most common conservative interventions to treat TMD.⁷ Among different physical therapy modalities, manual therapy can provide symptom and functional improvements¹⁰ including pain relief.^{11 31} Knowledge of predictive factors associated with good outcome to a specific intervention such as manual therapy applied to craniomandibular structures will facilitate clinical decision-making. Ultimately, such knowledge will lead to improved clinical and cost effectiveness of rehabilitation approaches.

Quality assurance

Only participants that have not received therapeutic intervention for their TMD in the last six months will be included in the current study. It is possible that such eligibility criteria could generate selection bias. To address this potential bias, the number of eligible and included subjects with the reason for non-participation will be documented.

Patient and public involvement

The research question in this study was developed following consultations and discussion with patients. Patients will not be involved in the analysis and data collection but will contribute to data interpretation and production of a lay summary of the findings.

Ethics and dissemination

The research protocol has been submitted to the Ethics Committee of the 'Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico' and subsequently will be submitted to the University of Birmingham Ethics Committee for approval. Researchers will inform all participants on the characteristics of the research and will obtain written consent. Participants will be informed that they are free to withdraw from the study at any time, without needing to provide reason. Any concerns for a participant by the study team will be fed back to the primary investigator (GA). Baseline characteristics of withdrawn participants will be compared with those of retained participants to assess for any differences. In the event of any unlikely adverse events, this will be immediately reported by the principal investigator to the ethics committee.

The results of this study will be submitted for publication in a peer review journal and presented at conferences.

Limitations

The study could potentially generate a non-representative sample of patients with TMD due to a possible selection bias. Subjects reporting other treatments before (6 months) and during the study will be excluded to minimise confounding bias and preserve internal validity. This could potentially generate a non-representative sample of TMDs because of exclusion of patients with high levels of pain which seek additional treatment. This potential event, associated with the fact that this observational study will be performed at a single site only, could reduce the external validity and the generalisability of the results.

CONCLUSION

This protocol paper describes what will be the first study to identify factors associated with pain reduction following manual therapy in patients with TMD. It is anticipated that the knowledge gained from the study described within this protocol, will facilitate clinical decision-making for manual therapists managing patients with TMD.

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Contributors GA, AEB and DF formulated the research question and study focus. GA drafted the initial version of the manuscript with DF, NRH, ABR, GB and ML provided guidance on topic, methodology and analyses. All authors reviewed and commented on each draft of the protocol. All authors have approved the final manuscript. DF is guarantor.

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